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Five-year incidence of cardiovascular disease and its predictors in Greece: the ATTICA study

Demosthenes B Panagiotakos¹, Christos Pitsavos², Christina Chrysohoou², Ioannis Skoumas² and Christodoulos Stefanadis²

Abstract: The 5-year incidence of cardiovascular disease (CVD) and its determinants, in a sample of men and women from Greece, was evaluated. From May 2001 to December 2002, 1514 men and 1528 women (> 18 years old) without any clinical evidence of CVD, living in the Attica area, Greece, were enrolled in the ATTICA study. In 2006, a group of experts performed the 5-year follow-up (941 of the 3042 (31%) participants were lost to follow-up). Development of CVD (coronary heart disease, acute coronary syndromes, stroke, or other CVD) during the follow-up period was defined according to WHO-ICD-10 criteria. The 5-year incidence of CVD was 11.0% in men and 6.1% in women ($p < 0.001$); the case fatality rate was 1.6%. Multi-adjusted logistic regression analysis revealed that increased age (odds ratio per year = 1.09, $p = 0.04$), waist-to-hip ratio (odds ratio = 5.07, $p = 0.02$), hypertension (odds ratio = 4.53, $p = 0.001$), diabetes (odds ratio = 4.53, $p = 0.001$) and C-reactive protein levels (odds ratio per 1 mg/dl = 1.31, $p = 0.02$) were the most significant baseline bio-clinical predictors of CVD. Furthermore, an increased education level and greater adherence to the Mediterranean diet (among 35–65-year-old individuals) were associated with a lower CVD incidence (odds ratio per 3 years of school difference = 0.83, $p < 0.001$ and odds ratio per 1/55 units in diet score = 0.94, $p < 0.001$), irrespective of various potential confounders. In conclusion, aging, central fat, hypertension and diabetes, inflammation process, low social status and abstinence from a Mediterranean diet seem to predict CVD events within a 5-year period.

Key words: cardiovascular; diet; education; epidemiology; hypercholesterolemia; incidence; inflammation

Introduction

It is well known that cardiovascular disease (CVD) is the leading cause of death and disability in the developed world. The American Heart Association and the National Heart, Lung, and Blood Institute reports that the cost for CVD in 2006 was estimated to be about \$400 billion.¹ Incidence of CVD varies from country to country, and culture to culture. For example, in a population-based Italian study,² the age-adjusted annual incidence of coronary heart disease (CHD) was about 3.7%, in a Japanese study the age-adjusted incidence of CHD increased from 0.4% during 1963 to 1970 to 1.5% during 1979 to 1986, and then was stable until 1994,³ while in the US, and according to the National Health and

Nutrition Examination studies, the annual age-standardized CVD incidence rates decreased from 29.3% (1971–1982) to 22.5% (1982–1992).⁴ It is important to mention that the aforementioned studies used similar criteria for defining CVD. According to the World Health Organization, unhealthy dietary habits, smoking and physical inactivity constitute the major, modifiable risk factors for the development of CVD, while increased arterial blood pressure, glucose and lipids levels, together with a low-grade inflammation process seem to promote the development of the disease.⁵ Furthermore, the investigators of the INTERHEART study reported that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity were the most significant factors associated with the risk of myocardial infarction worldwide in both sexes, and at all ages in all regions.⁶

Until now, the effect of various risk factors on CVD incidence in Greece has been mainly based on the findings from the Seven Countries study that started in the early 1960s. Given the lack of

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current data regarding the incidence of CVD in European, and especially south European, populations such as the Greek, the 5-year incidence of CVD (i.e. fatal or non-fatal acute coronary syndromes, stroke, or other CVD) and its determinants was investigated in a random sample of CVD-free adults.

Methods

Sampling procedure

The 'ATTICA' epidemiological study was carried out in the Attica area (including 78% urban and 22% rural regions) during 2001–2002. The sampling anticipated enrolling only one participant per household; it was random, multistage and based on the age (five strata) and sex (two strata) distribution of the Attica region (27 strata, census of 2001). At first, an invitation was sent to 4056 inhabitants from the above area, based on the census roll of each city. The invitation clarified that people with a history of CVD or living in institutions or having chronic viral infections should not participate in the sampling. Of the invited individuals, 3042 agreed to participate (75% participation rate); 1514 of the participants were men (18–87 years) and 1528 were women (18–89 years). All participants were interviewed by trained personnel (cardiologists, general practitioners, dieticians and nurses) who used a standard questionnaire. Exclusion of CVD was also performed through a detailed clinical evaluation by the study physicians, following standard criteria. The examination was performed in the individuals' homes. Further details about the aims, design and methods used in the ATTICA study may be found elsewhere in the literature.⁷

Baseline measurements

The baseline evaluation included information about: socio-demographic characteristics (age, sex, mean annual income and years of school), personal and family history of hypertension, hypercholesterolemia and diabetes, family history of CVD, dietary and other lifestyle habits (i.e. smoking status and physical activity). The evaluation of the nutritional habits was based on a validated semi-quantitative food-frequency questionnaire⁸: the EPIC-Greek questionnaire that was kindly provided by the Unit of Nutrition of Athens Medical School. All participants were asked to report the average intake (per week or day) of several food items that they consumed (during the last 12 months). Then, the frequency of consumption was quantified approximately in terms of the number of times a month a food was consumed. Any type of alcohol consump-

tion was measured in wine glasses (100 ml) and quantified by ethanol intake (in g per day). Based on the nutritional information, a special Mediterranean diet score was applied (range 0–55) that evaluates adherence to the Mediterranean diet.⁹ Moreover, smokers were defined as those who were smoking at least one cigarette per day during the past year or had recently stopped smoking (during the past year); the rest of the participants were defined as non-smokers. Pack-years were calculated as cigarette packs per day smoked by years of smoking. For the ascertainment of physical activity status the International Physical Activity Questionnaire (IPAQ¹⁰) was used as an index of weekly energy expenditure using frequency (times per week), duration (in minutes per time) and intensity of sports or other habits related to physical activity (in expended calories per time). Participants who did not report any physical activities were defined as physically inactive (sedentary lifestyle). Body mass index (BMI) was measured as weight (in kg) divided by standing height (m²). Obesity was defined as a BMI greater than 29.9 kg/m². Waist (in cm) and hip (in cm) circumferences were also measured. Arterial blood pressure (three recordings) was measured at the end of the physical examination with the individual in a sitting position. All participants rested for at least 30 minutes. Participants whose average blood pressure levels were greater or equal to 140/90 mmHg or were under antihypertensive medication were classified as having hypertension. Blood samples were collected from the antecubital vein between 8 and 10 am in a sitting position after 12 hours of fasting and alcohol abstinence. Total serum cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides were measured using a chromatographic enzymic method in a Technicon automatic analyser RA-1000 (Dade Behring, Marburg, Germany). Hypercholesterolemia was defined as total cholesterol levels greater than 200 mg/dl or the use of lipid-lowering agents. HDL-cholesterol was determined after precipitation of the apolipoprotein B-containing lipoproteins with dextran-magnesium-chloride. Serum for the measurement of these lipids was harvested immediately after admission. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula: (total cholesterol) – (HDL cholesterol) – 1/5 (triglycerides) (only in people who had triglyceride levels lower than 250 mg/dl). The intra and inter-assay coefficients of variation of cholesterol levels did not exceed 9%, triglycerides 4% and HDL 4%. Blood glucose levels (mg/dl) were measured with a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA, USA). Diabetes mellitus (type 2) was defined according to the American Diabetes Association diagnostic criteria (i.e. blood glucose levels greater than 125 mg/dl classified participants

as having diabetes). C-reactive protein and serum amyloid A were assayed by particle-enhanced immunonephelometry.

The Greek translation of the 20-item self-report State-Trait Anxiety Inventory (STAI), state version, was used to evaluate levels of anxiety.^{11,12} Total scores were based on the summation of the values assigned to each response (range: 20–80). Additionally, the Greek version of the Zung Self-Rating Depression Scale (ZDRS) was used in this work.^{13,14} The ZDRS is also a self-report test designed to quickly and easily quantify the presence and severity of depression.

Metabolic syndrome was defined by the recent NCEP ATP III criteria¹⁵ if three or more of the following risk factors were present: waist circumference ≥ 102 cm for men or ≥ 88 cm for women; triglyceride level ≥ 150 mg/dl; HDL-cholesterol level < 40 mg/dl for men or < 50 mg/dl for women; blood pressure $\geq 130/85$ mmHg; fasting glucose ≥ 100 mg/dl. Further details about the aims and procedures of the ATTICA epidemiological study may be found elsewhere.⁷

Follow-up

During 2006, the ATTICA study's investigators performed the 5-year follow-up. Of the 3042 initially enrolled participants, 2101 were found during the follow-up (69% participation rate). Of the individuals that were lost to follow-up (i.e. 941), 706 were not found because of missing or wrong addresses and telephone numbers that they had provided at the baseline examination and 235 because they denied being re-examined. No significant differences in the baseline characteristics were observed between those who participated to follow-up and those who did not participate regarding the distribution of age (45 ± 14 vs 45 ± 13 years, $p = 0.78$), sex (males 50% vs 50%, $p = 0.99$), years of school (12.1 ± 4 vs 12.0 ± 4 , $p = 0.67$), presence of hypertension (30% vs 28%, $p = 0.12$), diabetes (7% vs 6%, $p = 0.27$), hypercholesterolemia (39% vs 33%, $p = 0.10$), obesity (19% vs 15%, $p = 0.54$), as well as anxiety ($p = 0.20$) and depression levels ($p = 0.16$). However, those who participated in the follow-up were less likely to be smokers at baseline compared with those who were lost (41% vs 49%, $p < 0.001$).

In order to participate in the follow-up all participants were appointed through telephone calls (80% of the participants) or face-to-face interviews when their telephone number was not available, and asked to provide all their medical records to the study's investigators. Afterwards, the investigators performed a detailed evaluation of the participants' medical records (i.e. in the 2101 individuals that were found to follow-up). The following informa-

tion about participants was assessed: (a) vital status (death from any cause or due to CVD); (b) development of CHD (i.e. myocardial infarction, angina pectoris, other identified forms of ischemia – WHO-ICD coding 410–414.9, 427.2, 427.6-, heart failure of different types, and chronic arrhythmias – WHO-ICD coding 400.0–404.9, 427.0–427.5, 427.9-); (c) development of stroke (WHO-ICD coding 430–438); (d) development of hypertension, hypercholesterolemia and diabetes, as well as management of these conditions; (e) assessment of body weight and height; and (f) lifestyle habits, including physical activity and smoking status, as well as consumption of various food groups and beverages.

Statistical analysis

Incidence rates of CVD (CHD as defined above or stroke) were calculated as the ratio of new cases to the number of people who participated in the follow-up. Continuous variables are presented as mean values \pm standard deviation, and categorical variables are presented as frequencies. Associations between categorical variables were tested using the chi-squared test. Comparisons of mean values of normally distributed variables between those who developed an event and the rest of the participants were performed using Student's *t*-test, after controlling for equality of variances using the Levene's test. For some continuous variables that were not normally distributed (i.e. C-reactive protein levels, years of school) the Mann–Whitney non-parametric test was applied to evaluate the differences in the distributions of the skewed variables between those who developed a CVD event and the rest of the participants.

The relative risks of developing a CVD event during the 5-year period, according to the participants' baseline characteristics, were estimated using Cox proportional hazards models. The time to a CVD event was recorded on an annual basis. A stepwise procedure was applied. We used 5% as the cut-off for the probability of entering a variable in the model and 10% as the cut-off for the probability of removing a variable from the model. Interactions between sex and other covariates were tested in all steps, and when significant they remained in the model. Moreover, known confounders were also included in the model. A pseudo R^2 (Nagelkerke) was used to evaluate the explanatory ability of the predictive models.

To further explore which of the baseline measurements was the best predictor of CVD, discriminant analysis was performed using the area under the receiver operating characteristic curve (AUC; higher values of the AUC = better discriminating ability). Moreover, a cut-off point analysis using the ROC curve was used in order to determine the

optimal values of the baseline continuous factors that predict the event with the highest accuracy.

All reported *p*-values are based on two-sided tests and compared to a significance level of 5%. SPSS version 14 (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, USA) software was used for all the statistical calculations.

Results

Regarding the vital status of the 2101 individuals that participated in the follow-up, 1012 men and 1035 women were found alive, while 32 (3.0%) men and 22 (2.1%) women died during the 5-year period.

The 5-year incidence of CVD was 108 (11.0%) cases in men and 62 (6.1%) cases in women (*p* for sex difference < 0.001, the overall 5-year CVD event rate was 8.5%); 32 of these events were fatal (21 men, the 5-year CVD death rate was 1.6%). Causes of death were: myocardial infarction (25 cases), stroke (six cases) and other CVD (one case). Thus, the annual incidence of CVD was calculated to be 220 new cases per 10,000 men and 122 new cases per 10,000 women participants. A strongly significant linear trend was observed between incidence of CVD and baseline age of the participants (*p* for trend < 0.001, Table 1). In particular, men who were aged between 65 and 75 years at baseline examination experienced about a 10 times higher risk of developing CVD compared with those who were between 35 and 45 years, while the aforementioned relative risk in older women was about 18 times higher compared with those who were between 35 and 45 years. Furthermore, the overall men-to-women incidence rate ratio was 1.8; however, a gradual change according to participants' age was observed. In particular, the men-to-women ratio decreases consistently with age, starting from about 3:1 in younger people and became about 1:1 in those over 75 years (Table 1).

Demographic, clinical and behavioural characteristics of the participants by 5-year CVD status are presented in Table 2. Although, multiple comparisons are made in the presented results, and consequently the probability of false positives findings (i.e. *p*-value) increases dramatically, it is noticeable to mention that people who developed CVD were more likely to be older men, with increased blood lipids, systolic/diastolic blood pressure, glucose and C-reactive protein levels, as well as with lower adherence to the Mediterranean diet (i.e. lower diet score), but increased ethanol intake, body mass and waist-to-hip ratio, and lower education status, at baseline examination (all *p*-values < 0.009). Of the anthropometric indices waist-to-hip ratio had the best discriminating ability (AUC = 0.68), followed by waist circumference (AUC = 0.62), BMI (AUC = 0.64) and hip circumference (AUC = 0.60). Moreover, from the baseline biochemical measurements, ROC analysis showed that triglycerides (AUC = 0.645) followed by blood glucose (AUC = 0.626), C-reactive protein (AUC = 0.591), HDL-cholesterol (AUC = 0.587), total cholesterol (AUC = 0.584), and LDL-cholesterol (AUC = 0.569) were all significantly associated with the development of CVD (at *p* < 0.05). Additionally, cut-off point analysis based on the ROC curve showed that a waist-to-hip ratio greater than 0.94/0.82 for men and women, respectively (sensitivity 62%/69%, specificity 60%/66%), triglycerides greater than 125 mg/dl (sensitivity 53%, specificity 70%) and C-reactive protein levels greater than 1.6 mg/l (sensitivity 65%, specificity 51%) were the optimal cut-off values of these markers that predict with the highest accuracy the outcome. When the level of 3 mg/l was used as the cut-off for C-reactive protein the sensitivity decreased to 22% and the specificity increased to 82%.

However, all the aforementioned comparisons are prone to residual confounding; therefore, a multi-adjusted logistic regression analysis was performed. Based on this analysis, increased age (*p* < 0.001), waist-to-hip ratio (*p* = 0.003), C-reactive protein

Table 1 Five-year incidence of CVD in men and women from the ATTICA study, by age group

Age at baseline	Men (<i>n</i> ^a)	Women (<i>n</i> ^a)	Men-to-women incidence rate ratio
	5-year incidence of CVD		
< 35 years	2.5% (218)	0.0% (278)	>> 1
35–45 years	3.4% (270)	1.5% (271)	2.26
45–55 years	10.8% (309)	4.0% (254)	2.70
55–65 years	21.0% (140)	12.5% (131)	1.68
65–75 years	35.2% (51)	26.9% (78)	1.30
75+ years	43.8% (24)	42.3% (23)	1.03
Overall	11.0% (1012)	6.1% (1035)	1.80

^aPeople who participated in the follow-up examination.

Table 2 Characteristics of the ATTICA study's participants according to the 5-year incidence of CVD

	Baseline levels	Status at 5-year follow-up		<i>p</i>
		CVD event-free (<i>n</i> = 1826)	CVD events (<i>n</i> = 170)	
Age, years	45 ± 14	44 ± 13	60 ± 13	< 0.001
Male sex	50%	48%	64%	0.01
Years of school	12 ± 4	12 ± 3	10 ± 4	< 0.001
Smoking	43%	40%	30%	0.03
Physical activity	40%	42%	40%	0.63
Depression scale, ZDRS (20–80)	35 ± 7	35 ± 7	35 ± 8	0.87
Anxiety scale, STAI (20–80)	41 ± 11	40 ± 11	41 ± 8	0.93
Mediterranean diet score (0–55)	26 ± 7	26 ± 6	23 ± 7	0.001
Ethanol intake, g/d	12.4 ± 116	8.8 ± 13	15.1 ± 21	0.009
Systolic blood pressure, mmHg	123 ± 19	121 ± 17	134 ± 20	< 0.001
Diastolic blood pressure, mmHg	80 ± 24	79 ± 21	83 ± 18	< 0.001
Hypertension	30%	29%	58%	< 0.001
Total cholesterol, mg/dl	194 ± 42	193 ± 41	206 ± 44	< 0.001
Hypercholesterolemia	39%	39%	52%	0.001
Fasting glucose, mg/dl	93 ± 25	91 ± 22	104 ± 31	< 0.001
Diabetes	7%	5%	25%	< 0.001
Family history of CHD	28%	28%	34%	0.33
C-reactive protein, mg/l	1.93 ± 2.4	1.90 ± 2.3	2.42 ± 2.1	< 0.001
Metabolic syndrome	20%	20%	42%	< 0.001
Waist-to-hip ratio	0.86 ± 0.1	0.85 ± 0.1	0.92 ± 0.11	< 0.001
Body mass index, kg/m ²	26 ± 5	26 ± 4	28 ± 5	0.001
Obesity	18%	17%	30%	0.008
Abnormal waist (> 102/95 cm, m/f)	52%	52%	68%	< 0.001

STAI, State-Trait Anxiety Inventory; ZDRS, Zung Self-Rating Depression Scale.

levels ($p = 0.05$), presence of hypertension ($p = 0.05$) and diabetes ($p = 0.009$) were the most significant baseline predictors of developing CVD within a 5-year period. No significant interactions were observed between the previous factors and sex of the participants on the development of CVD. Moreover, the aforementioned baseline predictors were then used as binary variables, based on the previous cut-offs (i.e. waist-to-hip ratio above 0.94/0.82, C-reactive protein above 1.6 mg/l). Then a cumulative score was calculated (range 0–4). According to this score people who had all four conditions (i.e. waist-to-hip ratio above 0.94/0.82, C-reactive protein above 1.6 mg/l, hypertension and diabetes) experienced a 4.6 higher risk (95%CI 1.47–14.5) of developing CVD, after adjusting for various potential confounders. Moreover, low education status was also a significant predictor of CVD ($p = 0.033$). It is of interest that although smoking habits and physical inactivity increased the risk of CVD (see initial model presented in Table 3), these factors did not reach significance (at $p < 0.05$). These associations were further explored; the age-sex adjusted odds ratio of smoking was 1.02 per 40 pack-years ($p = 0.01$); however, when hypertension, hypercholesterolemia and diabetes were entered in the model, this relationship becomes insignificant. Moreover, the age-sex adjusted odds ratio of physical inactivity was 2.38 ($p = 0.001$); however, when

the waist-to-hip ratio and smoking habits were taken into account this relationship becomes insignificant.

The presence of the metabolic syndrome was then evaluated. After adjusting for age, sex, physical activity, smoking, and dietary habits, the presence of the metabolic syndrome was associated with a 2.09 times higher risk of developing a CVD event (95% CI 1.44–3.04). To test whether metabolic syndrome is a better predictor of future CVD events than the risk factors, we also estimated a model that contained age, sex, physical activity, smoking, dietary habits, and all the features of the syndrome. Based on the calculated pseudo R^2 statistics we observed that the two models had a similar explanatory ability (i.e. Nagelkerke R^2 of the model that is based on the metabolic syndrome = 23.8% and Nagelkerke R^2 of the model that is based on the individual components of the syndrome = 24.7%).

Regarding dietary habits, the Mediterranean diet score was inversely associated with the development of CVD (relative risk per 1 unit = 0.92; 95% CI 0.89–0.94, after adjustment for sex, physical activity status, smoking habits and other bio-clinical characteristics of the participants), but the relationship became insignificant when age was also included in the model. Thus, the analysis was repeated for different age groups. It was revealed that only in people aged between 35 and 65 years that greater

Table 3 Results from stepwise multiple logistic regression analysis that evaluated socio-demographic, lifestyle, biological, and clinical baseline characteristics in relation to the 5-year incidence of hypercholesterolemia in the ATTICA study participants

	Odds ratio	95% confidence interval
Initial multi-adjusted model		
Age (per 1 year)	1.06	1.04–1.08
Men versus women	1.42	0.83–2.44
Physically inactive versus physically active	1.16	0.74–1.82
Smokers versus non-smokers	1.12	0.69–1.83
Waist-to-hip ratio (per 0.1 unit)	1.22	0.97–1.54
Years of school (per 3 years)	0.80	0.68–0.97
Mediterranean diet score (per 1 unit)	0.94	0.90–0.97
Diabetes (y/n)	2.14	1.44–3.16
Hypercholesterolemia (y/n)	1.06	0.67–1.66
Triglycerides > 150 mg/dl (y/n)	1.05	0.65–1.70
Hypertension (y/n)	1.54	0.99–2.40
Family history of CHD	1.41	0.82–2.41
C-reactive protein (per 1 mg/l)	1.08	1.00–1.17
Final multi-adjusted model		
Age (per 1 year)	1.06	1.04–1.08
Waist-to-hip ratio (per 0.1 unit)	1.33	1.10–1.62
Years of school (per 3 years)	0.83	0.67–0.98
Hypertension (y/n)	1.55	0.99–2.41
Diabetes (y/n)	2.18	1.22–3.92
C-reactive protein (per 1 mg/l)	1.08	1.01–1.17

adherence to a Mediterranean diet was inversely associated with CVD incidence (relative risk per 1 unit = 0.94; 95% CI 0.90–0.97, after several adjustments were made), while no significant associations were observed among younger or older adults (p for homogeneity between odds ratios < 0.001).

Discussion

In this work the 5-year incidence rate of CVD was evaluated in a population-based sample of men and women from the Attica region of Greece. Approximately 8.5% of those who participated in the follow-up of the ATTICA study developed a fatal or non-fatal CVD event within this period. The men-to-women ratio was almost 3:1 in younger adults and become close to 1:1 in older adults. The annual incidence rate was about 2.2% in men and 1.2% in women, which means that about 550,000 people developed CVD during the preceding 5 years. These figures underline the burden of CVD in a 'low-risk' population. Of the baseline factors that were evaluated in this report, increased waist-to-hip ratio, the presence of hypertension and diabetes, and high C-reactive protein levels were the most significant bio-clinical predictors of CVD, while a low education level and lower adherence to the Mediterranean diet were also associated with increased CVD incidence rates. Furthermore, these findings reveal the importance of measuring the

waist-to-hip ratio as the most significant anthropometric predictor of future CVD events, emphasize the need to focus the prevention strategies on low educated people, underline the significance of the inflammation process in predicting CVD and confirm the cardioprotective effects of adherence to a healthy dietary pattern, such as the Mediterranean diet.

One of the main findings of this work is the strong association of the waist-to-hip ratio with the incidence of CVD. Discriminant analysis revealed that the waist-to-hip ratio had the best discriminating ability of all the anthropometric measurements. Obesity, abnormal waist circumference or waist-to-hip ratio have already been associated with the development of CHD and various metabolic disorders.^{16,17} Recently, the INTERHEART study⁶ investigators, based on a large case-control study, reported that abdominal obesity was one of the most significant risk factors of CHD in both sexes and in all parts of the world. The previous reports, together with our findings, underline the relative importance of waist-to-hip ratio compared with BMI or waist circumference in the prediction of future CVD events.

Moreover, the metabolic syndrome was also related to CVD in our work, irrespective of various potential confounders. However, the value of the metabolic syndrome as a scientific concept remains controversial, since several investigators suggest that the presence of the syndrome alone cannot predict global CVD risk, better than individual risk

factors, and especially abdominal obesity which is a marker of 'dysfunctional adipose tissue'.¹⁸ We have also observed similar findings, since the model that contained metabolic syndrome did not show better explanatory ability compared with the model that contained the individual features of the syndrome.

Low-grade systemic inflammation seems to participate in the pathobiology of obesity, insulin resistance, metabolic syndrome and CHD.^{19–22} Prospective cohort studies in healthy individuals revealed strong associations between elevated C-reactive protein levels and the risk of CVD events. Recently, Cushman *et al.*,²² in a 10-year follow-up reported that the relative risk of CHD for C-reactive protein levels greater than 3 mg/l compared with lower than 1 mg/l was 1.45, adjusting for various potential confounders, while the population-attributable risk of the disease for elevated C-reactive protein levels was 11%. In this work, baseline levels of C-reactive protein predicted CVD with good accuracy, irrespective of age, sex, smoking and dietary habits, as well as various other potential confounders (Table 3). It is of interest that cut-off point analysis revealed that the crucial level of C-reactive protein that better discriminates CVD events was 1.6 mg/l, which is much lower than the usual cut-off (i.e. 3 mg/l). Despite which should be the optimal cut-off for C-reactive protein, the present study, together with other reports, strongly suggest that this inflammatory marker should be included in the predictive models of CVD.

Diabetes and hypertension together with hypercholesterolemia constitutes major clinical risk factors for the development of CVD. In this work, both hypertension and diabetes showed a strong positive association with the development of CVD; in particular, hypertension increased by 55% the risk for CVD, while diabetes twofold the aforementioned risk, independently of the various other characteristics of the participants (Table 3). Both conditions promote the development of the metabolic syndrome, which is a current threat for CVD mortality and morbidity.²³ Wilson *et al.*, from the Framingham Heart Study, reported that the metabolic syndrome accounts for up to one-third of CVD in men over 8 years of follow-up. In particular, the metabolic syndrome's age-adjusted relative risk for CVD was found equal to 2.88 (95% CI 1.99–4.16) in men and equal to 2.25 (95% CI 1.31–3.88) in women.²⁴ In the present work, the metabolic syndrome was also strongly associated with the development of CVD within a 5-year period; specifically, the presence of the syndrome was associated with a 2.09-fold increase in the risk of a CVD event, irrespective of various potential confounders. Although hypercholesterolemia and hypertriglyceridemia showed a positive association with the development of CVD, this relationship did not reach significance when various characteristics of the participants were

taken into account (Table 3). Probably, the presence of the waist-to-hip ratio together with hypertension and diabetes excluded these disorders from the final predictive model (Table 3).

Based on several observational studies, the socio-economic status of people, as determined by occupation, education level and income, has been related to all-cause mortality and morbidity.^{25–28} Moreover, at the beginning of the twentieth century results from epidemiologic studies suggested that CVD was originally more common in the upper socio-economic class than the lower or middle class (i.e. a 'disease of affluence').¹ This hypothesis seems to fail nowadays. In our work, increased years of education was associated with a lower 5-year incidence of CVD in both sexes. It is of interest that the aforementioned association was independent of various clinical and lifestyle characteristics of the participants. Marmot and colleagues²⁸ have suggested that some intermediate factors between social class and CVD risk factors, such as high consumption of saturated fat, refined sugar and fiber, and smoking behavior may be responsible for the observed differences regarding the prevalence and the incidence of the disease among social classes. Previous reports from the ATTICA study²⁹ underlined that the inverse relationship observed between education status and prevalence of CVD risk factors was mainly explained by the adoption of an unhealthy lifestyle (including increased smoking habits, physical inactivity, obesity and non-compliance to medication) by individuals of low education. Nevertheless, the presented findings of the 5-year follow-up emphasize the need for special attention in people with a low education level in order to reduce the burden of CVD in the future.

An extensive body of scientific evidence relates diet and incidence of CVD.^{5,30–32} There is also increasing scientific evidence that there are protective health effects from diets which are high in the consumption of fruits, vegetables, legumes, whole grains, and which also include fish, nuts, and low-fat dairy products. The traditional Mediterranean diet, whose principal source of fat is olive oil, encompasses these dietary characteristics. Since the early 1970s, many investigators have recognized the beneficial role of this diet on CVD, metabolic disorders and several types of cancer.^{5,32} In the present work, greater adherence to the Mediterranean diet was associated with a lower 5-year CVD incidence, especially among middle-aged people. The previous relationship was independent from the potential confounding effect of various clinical and biochemical characteristics of the participants (Table 3). The lack of association in younger or older adults may be attributable to the fact that in people below 35

years of age there were very few cases of CVD, while in older adults the adherence to this traditional dietary pattern was high in most of the participants (as presented in previous reports from the ATTICA study³²). Finally, it should be mentioned that although smoking habits and physical inactivity increased the risk of CVD (see the initial model presented in Table 3), these factors did not reach statistical significance when the analysis was adjusted for various bio-clinical and other potential confounders. It seems that hypertension, hypercholesterolemia and diabetes masked the effect of smoking on CVD risk, while waist-to-hip ratio and smoking habits masked the effect of physical inactivity. Nevertheless, this insignificant effect should not underestimate its deleterious effect on the cardiovascular system as it has been shown in several other studies.

Limitations

The baseline evaluation was performed once, and may be prone to measurement error. Thus, the prevalence of various clinical risk factors or the levels of biological factors may have been overestimated. However, the applied methodology was similar to those of other prospective epidemiological studies in Europe and the USA, and therefore the results are comparable. Another limitation is that the dietary analysis for nutrient components (including electrolytes) was not completed, so the role of specific nutrients was not evaluated. Finally, telephone calls for the ascertainment of CVD are valid only when accurate medical records exist; thus, special attention was given to assess participants' medical files.

Conclusion

The present work evaluated factors associated with the development of CVD during a 5-year period in a Mediterranean population. Among several findings, multi-adjusted analysis revealed that waist circumference was the best anthropometric predictor for CVD events, a fact that may make the scientific community reconsider the role of BMI in cardiovascular risk evaluation. Moreover, low education level seems to predict CVD events; thus, people with a low social status are more likely to develop the disease, and therefore deserve more attention. Finally, adherence to the Mediterranean diet seems to be associated with a lower CVD event rate; although this is not entirely new, our finding is independent from various socio-demographic, clinical, inflammatory and other biochemical, as well as lifestyle characteristics of the participants.

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